

Fellström, B. C. et al. (2017) Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*, 389(10084), pp. 2117-2127. (doi: [10.1016/S0140-6736\(17\)30550-0](https://doi.org/10.1016/S0140-6736(17)30550-0))

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Deposited on: 31 March 2017

**Effects of a novel targeted-release formulation of budesonide vs. placebo in
IgA nephropathy: The NEFIGAN randomised clinical trial**

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Target journal: The Lancet

Word limit for RCTs: 4500; Currently 4252

Reference limit: 30; Currently 31

Figure/table limit: 5; Currently 5

Summary [[Word limit: 300; Currently 300]]

Background

IgA nephropathy (IgAN) is postulated to be associated with mucosal immune system dysfunction, manifesting as renal IgA deposition leading to impairment and end-stage renal disease (ESRD) in 20–40% of patients over 10–20 years. The NEFIGAN trial investigated a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver drug to the distal ileum in IgAN patients.

Methods

Randomised, double-blinded, placebo-controlled trial: 6-month run-in, 9-month treatment, 3-month follow-up phases. TRF-budesonide (16 mg/day [n=48]; 8 mg/day [n=51]) was compared with placebo (n=50) in patients with persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. Endpoints included mean change from baseline in urine protein creatinine ratio (UPCR) at 9 months (primary) and change in estimated glomerular filtration rate (eGFR). ClinicalTrials.gov number NCT01738035.

Findings

At 9 months, mean UPCR had decreased by -24.4% with TRF-budesonide (-27.3% with 16 mg/day [p=0.0092], non-significant -21.5% with 8 mg/day [p=0.0290]), relative to +2.7% with placebo. The effect was sustained throughout follow-up; mean UPCR decreased by -32.0% from baseline at 12 months for 16 mg/day vs. +0.5% for placebo. Over 9 months,

eGFR was stable with TRF-budesonide but decreased -9·8% with placebo (TRF-budesonide vs. placebo: $p=0\cdot0010$). There were dose-dependent trends in the incidence of solicited corticosteroid-related adverse events and discontinuations, although the incidence of all adverse events was 87·8%, 94·1%, and 84·0% with 16 mg/day, 8 mg/day, and placebo, respectively. Two of 13 serious adverse events were possibly related to TRF-budesonide: deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up.

Interpretation

TRF-budesonide, additional to optimised RAS blockade, reduced proteinuria and maintained eGFR in IgAN patients. Both these effects are indicative of a reduced risk of future progression to ESRD. These results suggest that TRF-budesonide has potential to become the first IgAN-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation.

Funding

Pharmalink AB

Introduction

Primary immunoglobulin A (IgA) nephropathy (IgAN) is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.¹ Approximately 20–40% of patients progress to end-stage renal disease (ESRD) within 10–20 years of diagnosis.^{2–4} Major risk factors for progression to ESRD are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).^{1,3,5,6} KDIGO guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade utilizing angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for IgAN patients with proteinuria >1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated up to the maximum recommended dose to achieve proteinuria <1 g/day (recommendation level 2D).⁷ For patients with persistent proteinuria >1 g/day and GFR >50 mL/min/1.73 m² despite 6 months' optimised RAS blockade, KDIGO suggest 6 months' treatment with high-dose systemic corticosteroids (recommendation level 2C).⁷ However, use of high-dose systemic corticosteroids is associated with increased risks of adverse events and sequelae including serious infections, hypertension, weight gain, diabetes, and osteoporosis.^{8–10} The benefit of systemic immunosuppression, in addition to the intervention of dietary restrictions and polypharmacy upon optimised RAS blockade has recently been questioned in the STOP-IgAN trial.¹¹ Notwithstanding, there is an unmet need for a targeted treatment with a favourable risk-benefit profile in IgAN patients at risk of progression to ESRD.

Evidence suggests a role for the mucosal immune system in the pathogenesis of IgAN.^{1,12,13} In IgAN patients, mucosal B lymphocytes located in Peyer's patches are thought to be primed to produce IgA1 that is galactose deficient (Gd-IgA1), which in the circulation can form large immune complexes with anti-glycan IgG antibodies.^{1,14–16} These complexes may bind to

glomerular mesangial cells and stimulate cell proliferation, release of inflammatory mediators that promote proteinuria, and fibrotic remodelling, ultimately leading to loss of renal function.^{1,15} This pathogenesis suggests that local immunosuppression of mucosal B lymphocyte activation and proliferation in Peyer's patches could attenuate Gd-IgA1 production,¹⁷ thereby reducing subsequent pathophysiological changes, assessed as a reduction in protein excretion by the kidneys.

A novel, oral, targeted-release formulation of the glucocorticosteroid budesonide (TRF-budesonide; NEFECON™ [Pharmalink AB, Stockholm, Sweden]) was developed to release drug in the distal ileum, where Peyer's patches reside at high density. The safety profile of TRF-budesonide was anticipated to be superior to high-dose systemic corticosteroids because of its extensive first pass metabolism: less than 10% of budesonide enters systemic circulation.¹⁸ In a previous exploratory phase 2a trial, 16 IgAN patients received TRF-budesonide (8 mg/day). Treatment over 6 months resulted in a statistically significant reduction in proteinuria and was well-tolerated.¹⁹ The objective of the current phase 2b trial was to evaluate the efficacy and safety of two doses of TRF-budesonide in IgAN patients at risk of progressing to ESRD due to persistent proteinuria despite optimised RAS blockade therapy.

Methods

Trial design

The NEFIGAN trial was randomised, double-blinded, and placebo-controlled in patients with biopsy-confirmed primary IgAN and overt proteinuria considered at risk of progressing to ESRD. This phase 2b trial was conducted at 62 sites across 10 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Italy, Spain, Sweden, The Netherlands, UK; see the Supplementary Appendix). Concerned competent authorities and ethics committees for participating centres approved the trial, which was conducted from December 2012 to June 2015 in accordance with Good Clinical Practice and the Declaration of Helsinki, 2008.

Patients

Male and female patients aged ≥ 18 years with biopsy-confirmed primary IgAN and overt proteinuria were eligible for the run-in phase. All patients provided written informed consent prior to enrolment. Inclusion criteria for randomisation to treatment included $\text{eGFR} \geq 45 \text{ mL/min/1.73 m}^2$ and a urine protein creatinine ratio (UPCR) $\geq 0.5 \text{ g/g}$ or urinary total protein $\geq 0.75 \text{ g/day}$, levels considered to increase risk of progressing to ESRD.²⁰ The approach of using either 24 hour protein excretion or UPCR to determine eligibility was applied to overcome collection errors and deviations from normal creatinine excretion (eg physically active and muscular males), respectively, thus minimizing the risk of unintentional exclusion of patients. Eligibility criteria are presented in Table S1.

Procedures

Trial medication was an oral capsule formulation of TRF-budesonide (NEFECON™; Pharmalink AB, Stockholm, Sweden) or placebo, designed to provide sustained release of

active compound that was delayed until the capsule reached the distal ileum,²¹ targeting where Peyer's patches reside at high density.

After screening, eligible patients were enrolled into a 6-month run-in phase, a 9-month treatment phase, and a 3-month follow-up phase; patient eligibility was assessed prior to run-in and treatment phases. During run-in, RAS blockade was optimised by up-titrating ACEIs and/or ARBs to a maximum recommended or tolerated dose, to a target blood pressure <130/80 mmHg, UPCR <0.5 g/g, and urine protein <0.75 g/day. At the end of run-in, patients with persistent proteinuria (UPCR \geq 0.5 g/g or proteinuria \geq 0.75 g/day) despite optimised RAS blockade, estimated GFR (eGFR [CKD-EPI serum creatinine equation²²]) or measured GFR \geq 45 mL/min/1.73 m², and blood pressure \leq 160/100 mmHg were eligible for randomisation to treatment. Run-in phase directives are detailed in the Supplementary Appendix.

An independent Data and Safety Monitoring Board (DSMB) monitored all safety issues and reviewed data at interim analysis.

Randomisation and masking

Patients were stratified according to baseline UPCR (\leq 0.9 g/g and $>$ 0.9 g/g) at Month 0 (baseline). Allocation of patients to treatment groups was done by randomisation using the method of randomly permuted blocks. Within each block, patients were allocated in a 1:1:1 ratio to TRF-budesonide 16 mg/day, 8 mg/day, or placebo. All patients continued optimised RAS blockade treatment throughout the trial. Randomisation was performed by Pharma Consulting Group AB, Uppsala, Sweden.

The trial was double-blind and the allocation to treatment groups was, therefore, unknown to the patient, the investigator, the sponsor, or the monitor. The sponsor and investigators were fully blinded to randomised treatment assignment and the pre-planned interim analysis.

To ensure blinding, placebo capsules were used with the same appearance and route of administration as the active capsules. Patients self-administered blinded capsules, once daily, 1 hour before breakfast during the treatment phase. During follow-up (Months 9–12), patients who received TRF-budesonide 16 mg/day during Months 0–9 were tapered to 8 mg/day for 2 weeks while all other patients (ie, those who received TRF-budesonide 8 mg/day or placebo during Months 0–9) received placebo to maintain blinding. No further trial medication was administered after tapering.

Treatment code envelopes were provided for each randomised patient. In case of emergency, the code envelope could be opened. Any unblinded patient had to be withdrawn from the trial.

Outcomes

The primary outcome was mean change from baseline in UPCR over the 9-month treatment phase. The primary analysis compared mean change from baseline in UPCR at 9 months between TRF-budesonide-treated patients (16 mg/day and 8 mg/day combined) and placebo-treated patients.

Key secondary and tertiary outcomes, assessed at various time points, included mean changes from baseline in eGFR; UPCR, 24-hour urine protein, urine albumin creatinine ratio (UACR), and 24-hour urine albumin were calculated from measured 24-hour urine samples; the presence or absence of microhaematuria, assessed by dipstick.

Standardised questionnaires were used at each visit to ask patients about the presence of specific gastrointestinal-related and corticosteroid-related adverse events. All solicited and spontaneously-reported adverse events were recorded from screening until the end of trial, and coded using the Medical Dictionary for Regulatory Activities (Version 16.0E). Vital signs, clinical chemistry, and haematology parameters were assessed.

Statistical analysis

Individual patient data from other relevant studies were used to estimate UPCR variability and the expected change from baseline at 9 months for placebo.^{23,24} The geometric mean ratio of 9 month:baseline UPCR values was 0.88 (log standard deviation [SD]: 0.597). The corresponding geometric mean ratio for TRF-budesonide was estimated from a previous exploratory phase 2a trial¹⁹ as 0.60 (log SD: 0.488). Sample size calculations were based on the hypothesis that the true difference between TRF-budesonide (16 mg/day and 8 mg/day combined) and placebo in log UPCR change from baseline was $\log(0.60) - \log(0.88)$ corresponding to an absolute difference of $(1-0.6) - (1-0.88) = 28\%$. A trial with 150 patients (50 per treatment arm) provided more than 90% power to detect this level of treatment effect for TRF-budesonide (16 mg/day and 8 mg/day combined) vs. placebo at the one-sided 2.5% alpha level.

The primary outcome (mean change from baseline in UPCR over the 9-month treatment phase) was assessed on the full analysis set (FAS), defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement (modified intention-to-treat analysis). A formal interim analysis governed by the DSMB was prospectively planned for when 90 patients completed 9 months' treatment, while the other patients in the FAS had entered the study but had not reached 9 months. Thus data from all randomised patients in the FAS, regardless of whether they had reach 9 months, was included

in the interim analysis, which was analysed using a mixed model repeated measures (MMRM) model. The threshold for significance for TRF-budesonide (16 mg/day and 8 mg/day) vs. placebo on the primary outcome was 1·58% one-sided; futility could also be declared if predictive power was $\leq 5\%$. The alpha level applied at final analysis was 1·52% one-sided to ensure an overall Type I error rate of 2·5% one-sided.

It was prospectively planned that if statistical significance for the primary outcome was met during the interim analysis: (a) the trial would continue; and (b) that during the final analysis (after all patients had completed the trial), confirmation of the interim analysis result would be gained by analysing the mean change from baseline in UPCR over the 9-month treatment and 3-month follow-up phases.

All secondary and tertiary endpoints were analysed during the final analysis. It was prospectively planned that all secondary and tertiary comparisons between treatment groups could only be made if statistical significance for the primary outcome was met during the interim analysis.

The following post-hoc analysis was defined after the interim analysis, and before the final database lock: The treatment effects on UPCR and eGFR CKD-EPI as a function of baseline UPCR and eGFR.

All efficacy data were analysed using MMRM analysis with fixed effect terms for baseline log UPCR, randomised treatment group, UPCR stratification level, visit, and visit by treatment group interaction. Subject and region were included as random effects. Region was defined on the country level, although Denmark was combined with Sweden (region = Scandinavia) and Belgium with the Netherlands (region = Benelux) due to small patient numbers per country.

215 Statistical analyses were performed by Scandinavian Development Services AB, Sweden,
216 using SAS® (Version 9.3).

217 This trial is registered with ClinicalTrials.gov, number NCT01738035.

218 **Role of the funding source**

219 The funder oversaw all study processes. Alex Mercer is an employee of the funder, who
220 participated in data analysis, data interpretation, and writing of the report. Both placebo and
221 TRF-budesonide treatments were provided by the funder. Data collection was performed by
222 Crown CRO Oy and Pharma Consulting Group AB. Statistical analysis was performed by
223 Scandinavian Development Services AB. Dr Kevin Carroll of KJC Statistics Ltd provided
224 statistical input and medical writing. Dr. Heather Cook of PharmaLogic Consulting AB
225 contributed to the study design, submissions for approval to concerned regulatory agencies,
226 data interpretation and writing of the report. Dr Ellen Robertshaw and Dr Justin Cook of
227 Niche Science and Technology Ltd and Dr Michael Riley of Trilogy Writing and Consulting
228 GmbH provided medical writing services, financed by the sponsor Pharmalink AB.
229 Following database lock and unblinding, the sponsor and all investigators had access to
230 analyses performed on trial data. The corresponding author was responsible for submitting
231 the manuscript for publication.

Results

In total, 297 patients were screened between December 11, 2012, and December 26, 2013, and 207 patients were enrolled into the run-in phase. Following run-in, all patients eligible for randomisation to treatment were receiving either a maximum tolerated or maximum recommended dose of ACEIs and/or ARBs. A total of 150 randomised patients received blinded trial medication; 149 comprised the FAS (one patient was unable to swallow capsules) (Figure 1 and Table S2). Trial drug exposure is described in the Supplementary Appendix. Treatment groups (TRF-budesonide 16 mg/day, 8 mg/day, and placebo) were well-balanced regarding demographic and baseline characteristics, with all patients using RAS blockade therapy (Table 1). Patients maintained optimised RAS blockade treatment throughout the trial. In a minority of patients, changes in dose or drug were made in RAS blockade (17 [11.3%] patients) or diuretics (10 [6.7%] patients). The frequencies of changes were comparable across the TRF-budesonide and placebo treatment groups (Table S3).

In the pre-planned interim analysis shown in Figure 2A, the primary outcome of geometric LS mean UPCR at 9 months was reduced from baseline by 24.4% (absolute change in UPCR to be presented) in all TRF-budesonide-treated patients combined versus an increase of 2.7% (absolute change in UPCR to be presented) in placebo-treated patients and the difference was statistically significant ($p=0.0066$) (Figure 2A; Note: all point estimates and 95% CIs in the following are presented in Table S4). Hence, the primary objective of the trial was met and the corresponding null hypotheses rejected. Geometric LS mean changes from baseline were -27.3% for TRF-budesonide 16 mg/day and -21.5% for 8 mg/day. The difference in UPCR at 9 months was statistically significant for TRF-budesonide 16 mg/day vs. placebo ($p=0.0092$), but not 8 mg/day vs. placebo ($p=0.0290$), which did not meet the adjusted p -

value at interim analysis ($p \leq 0.0158$). Change in UPCR from baseline at 9 months in the final analysis was consistent with the change in the interim analysis (Figure 2A) and is presented as absolute mean change in UPCR from baseline across the 12 months of the randomized portion of the study (Figure 2B).

In addition to the interim analysis performed when 90 patients had completed 9 months' treatment, a final analysis was also performed when all patients had completed the trial. In this final analysis, when assessed as a secondary outcome, reduction in UPCR at 9 months vs. baseline showed TRF-budesonide had a consistent effect on the relative change in UPCR regardless of baseline UPCR levels (Figure S1). Upon completion of the 3-month follow-up, the geometric LS mean reduction in UPCR was sustained in the TRF-budesonide 8 mg/day group (-22.6% change versus baseline) and continued to decrease in the 16 mg/day group (-32.0% change versus baseline) vs. an increase of 0.5% for placebo. Compared to placebo, the changes for both active treatment groups were statistically significant (16 mg/day vs. placebo, $p=0.0005$; 8 mg/day vs. placebo, $p=0.010$). Changes in 24-hour protein excretion, UACR, and 24-hour albumin excretion were consistent with the UPCR data (data not shown).

eGFR remained stable in the TRF-budesonide groups but decreased in the placebo-treated group during the treatment phase in the final analysis, as shown by percent changes at 9 months (Figure 3A) and by absolute mean changes in eGFR from baseline across the 12 months (Figure 3B). Mean percent change from baseline in eGFR at 9 months was -9.8% for placebo, +0.6% for 16 mg/day, and -0.9% for 8 mg/day (Figure 3A). Comparisons with placebo achieved statistical significance at 9 months (16 mg/day vs. placebo: $p=0.0026$; 8 mg/day vs. placebo: $p=0.0064$). Exploratory post-hoc analyses suggested that stabilisation of eGFR in TRF-budesonide-treated groups was independent of baseline UPCR and eGFR values, and that the degree of eGFR reduction in the placebo group appeared related to the

280 magnitude of baseline UPCR (Figure S1). eGFR levels in the TRF-budesonide 16 mg/day
 281 group were sustained throughout the trial (mean percent change from baseline at
 282 12 months: -0.7 vs. -10.9% for placebo; $p=0.0134$).

283 When assessed as a tertiary outcome in the final analysis, the proportion of patients with
 284 microhaematuria in the TRF-budesonide 16 mg/day group decreased from 87.5% ($n=42$ of
 285 48) at baseline to 43.8% ($n=21$ of 48) at 9 months, and was statistically significant versus
 286 placebo (74.0% [$n=37$ of 50] of placebo-treated at 9 months, 95%CI 0.072-0.675, **OR 0.221**,
 287 $p=0.0041$) but remained unchanged in the 8 mg/day-and placebo-treated groups.

288 There were no deaths and no patient progressed to ESRD. Fourteen patients
 289 (TRF-budesonide 16 mg/day, $n=3$; 8 mg/day, $n=4$; placebo, $n=7$) reported
 290 treatment-emergent adverse events associated with worsening of renal function and/or
 291 received high-dose systemic corticosteroid therapy.

292 Eleven patients reported 13 treatment-emergent serious adverse events (Table S5). Two were
 293 considered possibly related to TRF-budesonide by investigators blinded to study treatment:
 294 deep vein thrombosis (16 mg/day), and unexplained worsening of renal function, reported
 295 during follow-up after tapering from 16 mg/day to 8 mg/day. Two serious adverse events in
 296 the placebo-treated group were considered possibly related to trial medication: both cases of
 297 increased proteinuria, one with a decline in renal function (see the Supplementary Appendix
 298 for details on adverse event reporting).

299 The total incidence of treatment-emergent adverse events was similar across treatment groups
 300 (Table 2). The most frequently reported adverse event, nasopharyngitis, was reported by
 301 similar percentages of patients in each group. There were no statistically significant changes
 302 from baseline in body weight, blood pressure, or glycated haemoglobin A1c (HbA_{1c}) values in
 303 either TRF-budesonide group vs. placebo at end of treatment (Table S6, post-hoc analysis).

304 Two patients receiving TRF-budesonide, both with a body mass index of 36 kg/m² at
305 baseline, exhibited increases in HbA_{1c} into the diabetic range (≥ 48 mmol/mol) at the end of
306 treatment or during follow-up (Table S6 footnote for details). There were no other clinically
307 relevant changes in clinical chemistry variables in any treatment group (see the adverse event
308 reporting section of the Supplementary Appendix for the list of clinical chemistry variables
309 investigated). The incidence of gastrointestinal-related adverse events was similar in
310 TRF-budesonide-treated and placebo-treated patients (Table S7).

311 Solicited corticosteroid-related adverse events were more frequently reported by
312 TRF-budesonide-treated patients (Table S8). Eighteen patients experienced adverse events
313 that led to discontinuation of treatment (n=11 in the 16 mg/day group, n=5 in the 8 mg/day
314 group, n=2 in the placebo group). The majority of patients who discontinued in the
315 TRF-budesonide groups experienced corticosteroid-related adverse events (Table S9).

Discussion

We report the results of the NEFIGAN trial in which 9 months' treatment with TRF-budesonide resulted in a statistically significant reduction in UPCR vs. placebo in patients with primary IgAN. This primary outcome was met in a pre-specified interim analysis of data from the FAS population. The effect of TRF-budesonide was shown to be dose- and time-dependent. Upon completion of the 3 month follow up, the mean percent reduction in UPCR was sustained in the TRF budesonide 8 mg/day group and continued to decrease in the 16 mg/day group. This persistence of effect following cessation of treatment is suggestive of a disease-modifying effect. There is a growing body of evidence and general acceptance that a reduction in proteinuria is associated with a reduced risk of ESRD in IgAN patients, and time-averaged (TA)-proteinuria is predictive of renal survival in IgAN patients: the rate of decline of renal function and subsequent risk of renal failure are associated with higher levels of TA-proteinuria.^{5,20} A recent meta-analysis of IgAN trials used contemporary statistical methodology to assess the possible surrogacy of the effect of treatment intervention (RAS blockade, fish oil, immunosuppression, and steroids) on proteinuria at 9 months to predict the effect of the intervention on ESRD clinical outcome. The analysis showed a statistically significant association, suggesting that an improvement in proteinuria at 9 months for drug compared to control would be positively associated with an improvement in longer term ESRD outcome.²⁵

Patients entering the treatment phase of this trial were at risk of progression to ESRD due to persistent proteinuria despite optimised RAS blockade. The further reduction in proteinuria was achieved by targeting an alternative pharmacological mechanism, and was attributable to TRF-budesonide, irrespective of baseline UPCR, eGFR and time since diagnosis of IgAN (Fig S1D). Our findings support the generally accepted hypothesis that mucosal immune

system dysfunction has a significant role in the pathogenesis of IgAN, as TRF-budesonide targets the region of the gastrointestinal tract where Peyer's patches reside at high density.

eGFR declined in the placebo-treated group but remained stable in the TRF-budesonide groups following 9 months' treatment, an effect that persisted throughout follow-up in the 16 mg/day group. Stabilisation of eGFR in IgAN patients is likely to predict a favourable outcome. It should be noted that RAS blockade therapy remained optimised throughout the trial, with no dose changes during the treatment phase, except in a small number of individuals (dose of RAS blockade was increased for 5/150 patients and decreased for 6/150 patients), distributed across the 3 treatment groups (see Table S3). Despite the rigorous maintenance of RAS blockade, the rapid rate of loss of eGFR observed in the placebo-treated group was greater than that seen in the recently reported STOP-IGAN study¹¹ but consistent with other studies of IgAN in patients receiving optimised RAS blockade, albeit with generally higher levels of baseline proteinuria.^{24,26} Of note, posthoc analysis demonstrated that eGFR reduction in the placebo group was related to baseline proteinuria (Fig S1B), (but not to baseline blood pressure ? (not shown) ?Is this correct ? I did not see any stat.analysis on that ?) As histology data are not available for all of these studies, it is difficult to speculate on the contribution of histopathological changes to rate of eGFR decline. However, the deterioration in eGFR illustrates that this patient population is at risk of disease progression, current standard-of-care therapy is insufficient, and there is a need for further intervention in IgAN patients with persistent proteinuria.

High-dose systemic corticosteroids and other potent immunosuppressive treatments have been studied in a number of randomised controlled trials with varying results.²⁷ A consequence of these trials has been the necessity to test interventions with a background of optimised standard-of-care RAS blockade, as has been conducted in this trial. This has also been applied in the TESTING trial, a randomised controlled trial evaluating high-dose

systemic corticosteroid therapy vs. placebo (recruitment was stopped early and randomised treatment discontinued due to safety concerns, interim results published)³², and in the STOP-IgAN trial.¹¹ The STOP-IgAN trial assessed the potential benefit of systemic immunosuppression in addition to the intervention of dietary restrictions and polypharmacy upon optimised RAS blockade, and is the first study in IgAN to employ such comprehensive supportive care. No difference in the rate of decrease in eGFR was observed between groups over the 3-year period of the STOP-IgAN trial.¹¹ The slow annual loss of eGFR in the intensive supportive care group (1.6 mL/min/1.73 m²) suggests that further interventions, in addition to optimised RAS blockade, retards the loss of renal function.¹¹

TRF-budesonide 16 mg/day resulted in a statistically significant reduction in the presence of microhaematuria at 9 months vs. placebo. Although the prognostic significance of haematuria disappearance in IgAN has not been prospectively investigated, clinical and experimental studies suggest that haematuria is associated with glomerular and tubulointerstitial damage in IgAN and other glomerular diseases.^{28,29}

In the present trial, TRF-budesonide appeared to be safe and generally well-tolerated, although there was a dose-dependent trend in the incidence of solicited corticosteroid-related adverse events and in discontinuations due to these events (see Tables S8 and S9). Budesonide, administered as a targeted-release oral dosage form, is subject to high first-pass metabolism, resulting in low systemic exposure (approximately 10% of administered dose).¹⁸ Some degree of systemic exposure is reflected in reduced cortisol excretion (data not shown) and the aforementioned dose-dependent trend in the incidence of solicited corticosteroid-related adverse events. However, several studies have reported higher incidences of diabetes mellitus or impaired glucose tolerance, hypertension, and weight gain in high-dose systemic corticosteroid-treated patients.^{11,30} Furthermore, increased incidences

of serious and fatal infections were documented with high-dose systemic immunosuppressive therapy in the STOP-IgAN trial¹¹ and TESTING trial³². In contrast, no serious infections were attributed to TRF-budesonide in the NEFIGAN trial and there were no statistically significant changes in blood pressure, HbA_{1c}, or body weight with TRF-budesonide vs. placebo. There was a trend for numerically higher systolic and diastolic blood pressure levels in the TRF-budesonide 16 mg group at the end of treatment compared to baseline values, but this was not statistically significant (Table S6). The NEFIGAN trial data indicate that TRF-budesonide may elicit fewer and less severe systemic effects and has a preferable tolerability profile than previously reported for high-dose systemic corticosteroid regimens, when used to treat IgAN patients at risk of progression to ESRD, many of whom are young adults.^{11,30} However, this needs to be confirmed in larger studies than the current phase 2b trial.

Proteinuria is a major risk factor for renal failure in IgAN.^{3,5} As addressed by Rauen et al.,¹¹ in the past, clinically significant proteinuria has been arbitrarily defined as an excretion level greater than 1 g/day (KDIGO guidelines).⁷ However, evidence from epidemiology studies indicate that IgAN patients with proteinuria of 0.5 to 1 g/day are at increased risk of renal failure.^{20,31} Thus, to evaluate TRF-budesonide in a clinically relevant high-risk IgAN population, a proteinuria threshold of either 0.75 g/day or 0.5 g/g UPCR (on a 24-hour collection) was selected. A threshold level of 0.75 g/day was similarly applied in the recently reported STOP-IgAN trial.

The primary objective of this trial was to assess the effect of TRF-budesonide on UPCR, a proteinuria-based measure and surrogate endpoint for renal failure. While both a reduction in UPCR and stabilisation of eGFR were demonstrated, it will be necessary to quantify the magnitude of relative risk reduction associated with TRF-budesonide-treatment in IgAN

patients at risk of progression to ESRD in a larger trial of longer duration. Another limitation of the present trial is that the patient population treated was almost exclusively Caucasian. In addition, allowing entry of patients in to the study regardless of time since biopsy, led to a lack of availability of recent histopathology data on all patients prior to randomization prevented the implementation of a stratification strategy to discount imbalance of renal histology score as a potential confounder. However, in a post-hoc analysis, a consistent effect on relative change in UPCR at 9 months was observed regardless of time from diagnosis (Figure S1d) indicating that this did not affect the results. There are also no published pharmacokinetic data for TRF-budesonide in patients with IgAN. Patients with severe hepatic impairment were excluded from the study but it is unknown if IgAN patients may be subject to higher systemic exposure due to increased mucosal GI absorption. There is evidence of increased exposure of budesonide in chronic inflammatory bowel disease (range 11-21% vs. 9-12% in healthy volunteers) but that systemic exposure normalises after 8 weeks of treatment³³. Nevertheless, this trial is one of the largest randomised controlled trials conducted in IgAN in which RAS blockade was optimised prior to adjunct therapy.

This trial demonstrated that 9 months' treatment with TRF-budesonide resulted in reduced proteinuria and stabilised eGFR in IgAN patients at risk of progression to ESRD. The observed effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in IgAN patients with persistent proteinuria.

TRF-budesonide has the potential to become the first disease-specific treatment for IgAN, with a risk-benefit profile supportive of its use early in the course of disease.

Research in context

Evidence before this trial

We searched PubMed up to April 26, 2016, for published papers about NEFECON using the following search terms (with no language restrictions): “targeted-release”, “budesonide”, “TRF-budesonide”, and “NEFECON”. We identified one relevant paper. In 2011, Smerud and colleagues¹⁹ reported an open-label, uncontrolled, exploratory phase 2a trial, in which 16 IgAN patients received TRF-budesonide. Treatment over 6 months resulted in a statistically significant reduction in proteinuria and was well tolerated.¹⁹

Added value of this trial

To date, the current phase 2b trial is the only randomised, double-blinded, placebo-controlled trial to investigate and demonstrate that TRF-budesonide, additional to optimised RAS blockade, reduced proteinuria and stabilised eGFR in IgAN patients at risk of progression to ESRD. At 9 months, mean UPCR had decreased by 24·4% in all TRF budesonide-treated patients combined versus an increase of 2·7% in placebo-treated patients (combined TRF budesonide vs. placebo: $p=0\cdot0066$). The effect was sustained throughout follow-up for 16 mg/day; mean UPCR decreased 32·0% from baseline at 12 months vs. 0·5% for placebo. Over 9 months, eGFR was stable with TRF-budesonide but decreased 9·8% with placebo (combined TRF-budesonide vs. placebo: $p=0\cdot0010$). Both these effects are indicative of a reduced risk of future progression to ESRD.

Implications of all the available evidence

TRF-budesonide has the potential to become the first IgAN-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation, reducing the risk of progression to ESRD.

Contributors

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459 Floege, Alan G. Jardine, Francesco Locatelli, Bart D. Maes, Alex Mercer, Manuel Praga,
460 Søren S. Sørensen, and Vladimir Tesar designed the study. Bengt C. Fellström, Jonathan
461 Barratt, Johan W. de Fijter, Jürgen Floege, Gerd Hetzel, Bart D. Maes, Fernanda Ortiz,
462 Manuel Praga, Søren S. Sørensen, Vladimir Tesar and Lucia Del Vecchio were study
463 investigators. Bengt C. Fellström was the principal investigator. All authors contributed to
464 data interpretation, writing, manuscript review and approval of the final version.

465 **Declaration of interests**

466 Bengt C. Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, Francesco Locatelli,
467 Johan de Fijter, Jürgen Floege, Bart Maes, Manuel Praga, and Vladimir Tesar had a
468 consultancy agreement in place with Pharmalink AB and received payment for their services.
469 Bengt C. Fellström is also a shareholder (<1% of all shares) in Pharmalink AB. Alex Mercer
470 is an employee of Pharmalink AB. All other authors have no major financial conflicts of
471 interest to be disclosed.

472 **Acknowledgements**

473 The authors would like to thank the investigators, nurses, patients, and other participants. A
474 full list of investigators and trial sites is included in the Supplementary Appendix.

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Table 1: Patient demographics and baseline characteristics* (full analysis set)

Variable		Placebo (N=50)	TRF-budesonide 8 mg/day (N=51)	TRF-budesonide 16 mg/day (N=48)	Total (N=149)
Age (years)		38.9 (12.0)	40.6 (13.0)	37.5 (11.9)	39.0 (12.3)
Sex, n (%)	Male	35 (70.0)	37 (72.5)	33 (68.8)	105 (70.5)
BMI (kg/m ²)		27.5 (5.37)	26.5 (4.39)	27.8 (5.17)	27.3 (4.99)
Weight (kg)		85.2 (18.89)	80.9 (14.46)	86.7 (16.89)	84.2 (16.89)
Race, n (%)	Asian	1 (2.0)	0	1 (2.1)	2 (1.3)
	Caucasian	48 (96.0)	49 (96.1)	47 (97.9)	144 (96.6)
	Other	1 (2.0)	2 (3.9)	0	3 (2.0)
	Hispanic/Latino	3 (6.0)	11 (21.6)	7 (14.6)	21 (14.1)
Ethnicity, n (%)	Non-Hispanic/Non-Latino	47 (94.0)	40 (78.4)	41 (85.4)	128 (85.9)
Blood pressure (mmHg)	Systolic	128.1 (11.87)	127.7 (13.56)	126.7 (11.62)	127.5 (12.33)
	Diastolic	80.2 (10.13)	80.3 (9.66)	78.1 (9.59)	79.6 (9.78)
UPCR (g/g), median (range)		0.83 (0.33–4.12)	0.81 (0.26–3.00)	0.79 (0.22–2.10)	0.81 (0.22–4.12)
24-hour protein (g/day), median (range)		1.23 (0.57–9.75)	1.14 (0.44–3.31)	1.32 (0.41–10.66)	1.2 (0.41–10.66)
eGFR CKD-EPI (creatinine formula) (mL/min/1.73 m ²)		76.5 (23.2)	74.1 (25.8)	83.8 (25.9)	78.3 (25.1)
Patients with microhaematuria, n (%)		40 (80.0)	32 (62.7)	42 (87.5)	114 (76.5)
Time from diagnosis to start of treatment (days), median (range)		1101 (202-8153)	1972 (209-7833)	1218.5 (186-11048)	1499 (186-11048)
Patients previously treated with corticosteroids/immunosuppressants, n (%)		7 (14.0)	14 (27.5)	6 (12.5)	27 (18.1)
Patients on ACEI alone, n (%) [% on maximum recommended dose]		21 (42.0) [28.0]	25 (49.0) [21.6]	26 (52.4) [29.2]	72 (48.3) [26.2]
Patients on ARB alone, n (%) [% on maximum recommended dose]		16 (32.0) [20.0]	14 (27.5) [15.7]	14 (29.2) [18.8]	44 (29.5) [18.1]
Patients on ACEI and ARB, n (%) [% on maximum recommended dose]		13 (26.0) [6.0]	12 (23.5) [3.9]	8 (16.7) [4.2]	33 (22.1) [4.7]
Patients who made lifestyle changes during the run-in phase, n (%)†		16 (32.0)	18 (35.3)	14 (29.2)	48 (32.2)

*Unless otherwise indicated, values are expressed as mean (standard deviation).

†Including salt intake, fluid intake, protein intake, fish oil intake, smoking, exercise.

ACEI=angiotensin-converting-enzyme inhibitor. ARB=angiotensin receptor blocker. BMI=body mass index. CKD-EPI=chronic kidney disease epidemiology collaboration equation. UPCR=urine protein creatinine ratio.

Table 2: Treatment-emergent adverse events reported by $\geq 5\%$ of all patients by preferred term (safety set)*

Preferred Term	Placebo (N=50)		TRF-budesonide 8 mg/day (N=51)		TRF-budesonide 16 mg/day (N=49)		Total (N=150)	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any AE	42 (84)	162	48 (94)	270	43 (88)	305	133 (88)	737
Nasopharyngitis	10 (20)	14	8 (16)	16	10 (20)	16	28 (19)	46
Acne‡	3 (6)	3	8 (16)	9	9 (18)	10	20 (13)	22
Joint swelling	2 (4)	2	8 (16)	8	9 (18)	14	19 (13)	24
Cushingoid‡	3 (6)	3	5 (10)	5	8 (16)	8	16 (11)	16
Insomnia‡	2 (4)	2	6 (12)	6	8 (16)	9	16 (11)	17
Diarrhoea	7 (14)	9	1 (2)	1	5 (10)	5	13 (9)	15
Dyspepsia†	4 (8)	5	2 (4)	2	7 (14)	9	13 (9)	16
Headache	3 (6)	4	3 (6)	3	6 (12)	6	12 (8)	13
Alopecia‡	2 (4)	2	4 (8)	5	4 (8)	4	10 (7)	11
Back pain	1 (2)	1	6 (12)	8	3 (6)	3	10 (7)	12
Mood swings‡	2 (4)	2	3 (6)	3	5 (10)	5	10 (7)	10
Oedema peripheral	2 (4)	3	2 (4)	3	6 (12)	9	10 (7)	15
Blood creatine phosphokinase increased	3 (6)	3	3 (6)	4	3 (6)	3	9 (6)	10
Hirsutism‡	1 (2)	1	3 (6)	3	5 (10)	5	9 (6)	9
Hypertension	1 (2)	1	3 (6)	3	5 (10)	5	9 (6)	9
Muscle spasms	2 (4)	3	5 (10)	5	2 (4)	2	9 (6)	10
Abdominal pain†	1 (2)	1	4 (8)	4	3 (6)	4	8 (5)	9
Nausea	1 (2)	1	4 (8)	4	3 (6)	5	8 (5)	10
Upper respiratory tract infection	3 (6)	3	2 (4)	3	3 (6)	3	8 (5)	9

*Table displays adverse events reported by $\geq 5\%$ of the total patient population.

†Gastrointestinal-related adverse events solicited by questionnaire at every visit.

‡Corticosteroid-related adverse events solicited by questionnaire at every visit.

AE=adverse event. n=number of patients. e=number of events.

Figure 1: Patient CONSORT diagram

Flow diagram of all patients screened, enrolled, and randomised with reasons for withdrawal.

*FAS corresponds to the modified intention-to-treat analysis set.

ACEI=angiotensin-converting enzyme inhibitors. AE=adverse event. ARBs=angiotensin receptor blockers. CTP=clinical trial protocol. FAS=full analysis set. SAE=serious adverse event.

Figure 2: Change in UPCR from baseline

Panel A shows the percent change in UPCR from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months at the interim analysis (primary outcome). The comparisons of TRF-budesonide 16 mg/day and 8 mg/day combined and 16 mg/day with placebo were statistically significant, but not 8 mg/day vs. placebo ($p=0.0290$). Panel B shows the absolute mean change in UPCR from baseline in patients receiving TRF-budesonide 16 mg/day, 8 mg/day, or placebo over the 9 month treatment phase (solid line) and 3 month follow-up phase (dashed line).

UPCR=urine protein creatinine ratio. Data are expressed as mean \pm standard error of the mean.

In both panels, the changes in UPCR are based on data from all 149 patients in the FAS.

Figure 3: Change in eGFR from baseline

Panel A shows the percent change in eGFR CKD-EPI from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months. The comparisons of TRF-budesonide 16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day with placebo were statistically significant. Panel B shows the absolute mean change in eGFR CKD-EPI from baseline in patients receiving TRF-budesonide 16 mg/day, 8 mg/day or placebo over the 9 month treatment phase (solid line) and 3 month follow-up phase (dashed line). CKD-EPI=chronic kidney disease

epidemiology collaboration equation. eGFR=estimated glomerular filtration rate. Data are expressed as mean \pm standard error of the mean. In both panels, the changes in UPCR are based on data from all 149 patients in the FAS.

Figure 1

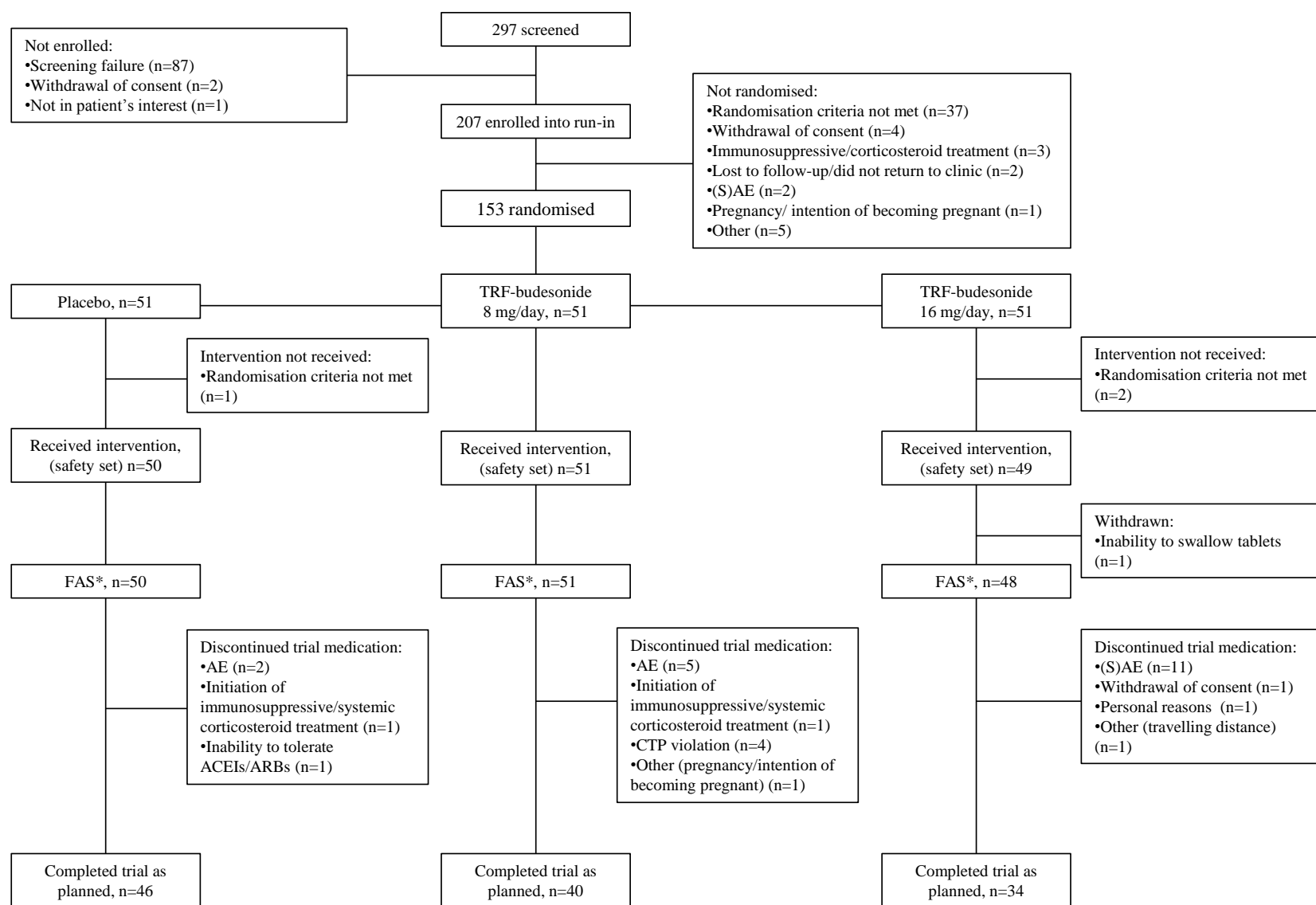
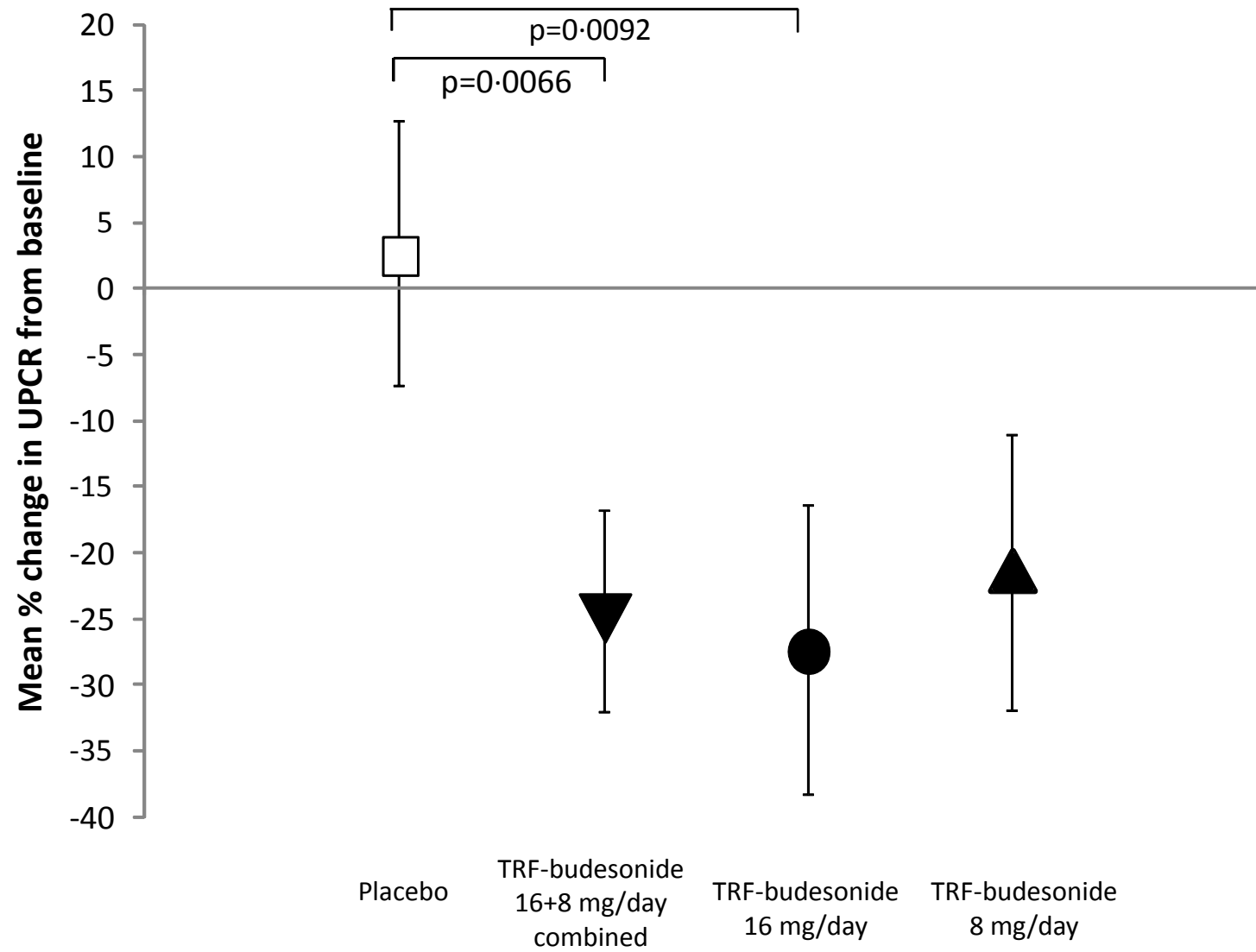


Figure 2

A



B

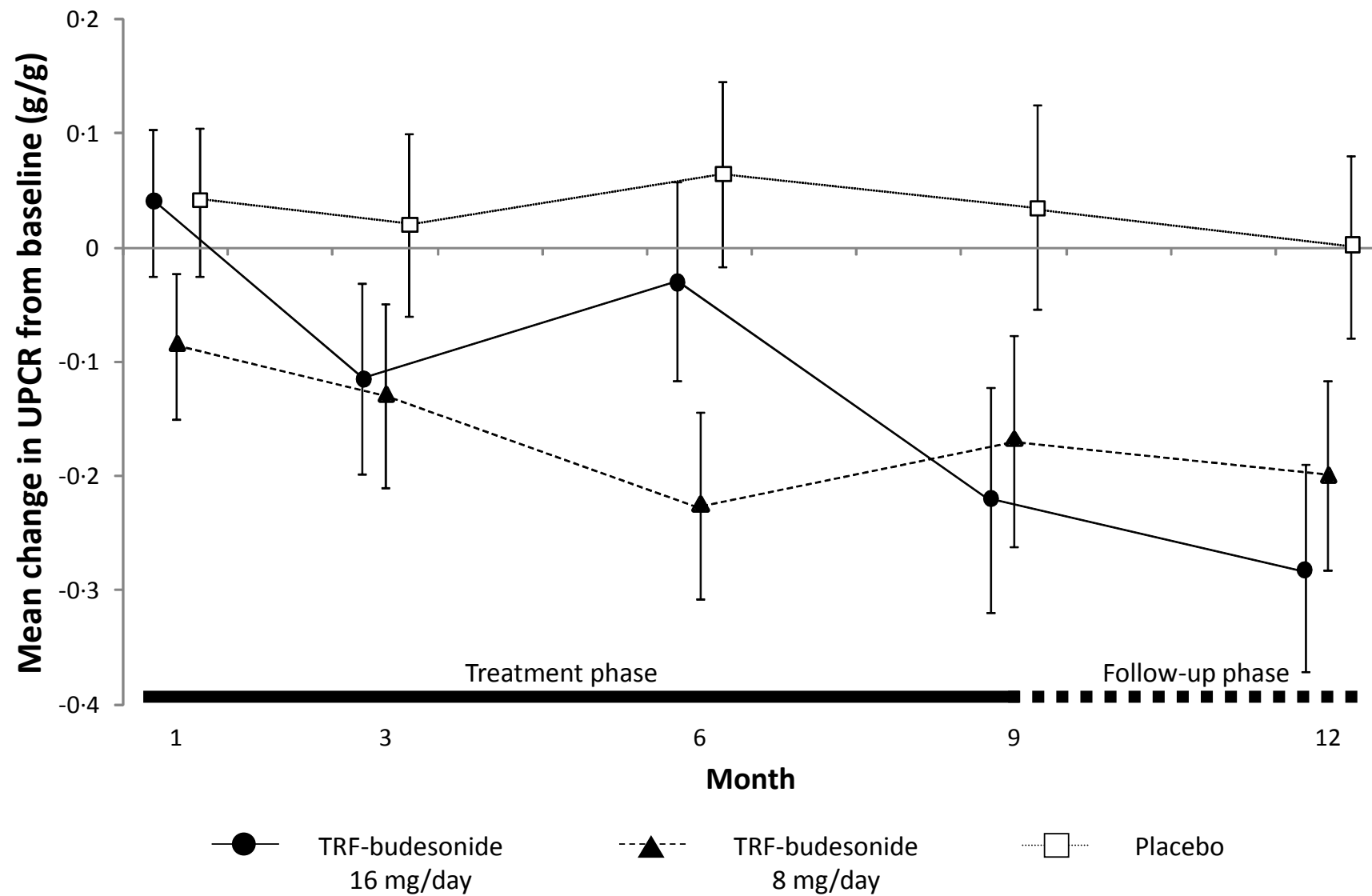
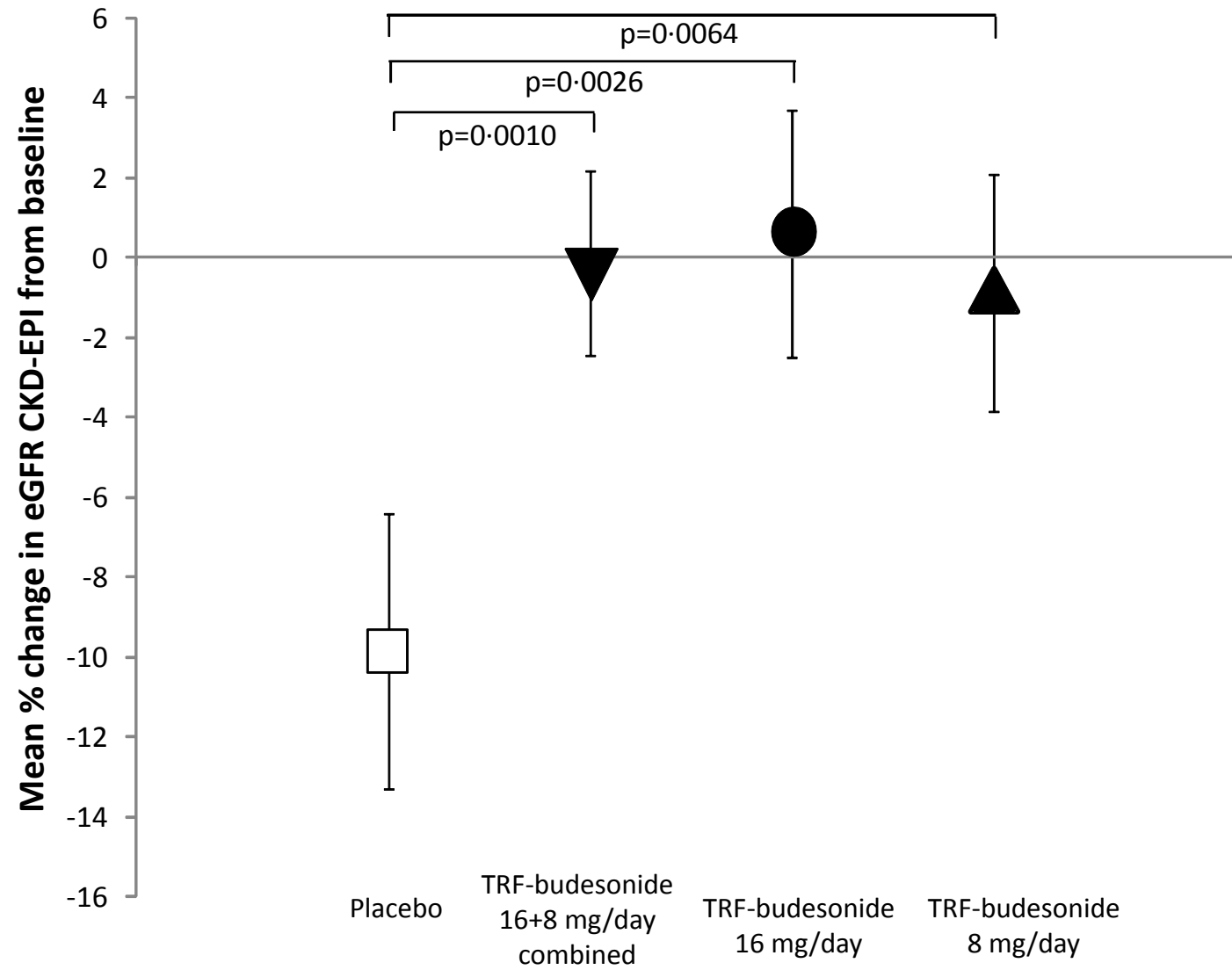


Figure 3

A



B

